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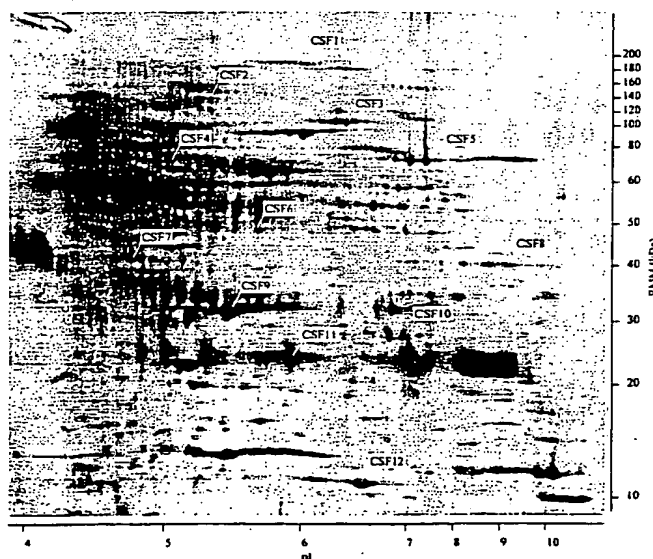
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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
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[Continued on next page]

(54) Title: PROTEINS, GENES AND THEIR USE FOR DIAGNOSIS AND TREATMENT OF VASCULAR DEMENTIA



(57) Abstract: The present invention provides methods and compositions for screening, diagnosis and prognosis of Vascular Dementia, for monitoring the effectiveness of Vascular Dementia treatment, identifying patients most likely to respond to a particular therapeutic treatment and for drug development. Vascular Dementia-Associated Features (VFs), detectable by two-dimensional electrophoresis of cerebrospinal fluid, serum or plasma are described. The invention further provides Vascular Dementia-Associated Protein Isoforms (VPIs) detectable in cerebrospinal fluid, serum or plasma, preparations comprising isolated VPIs, antibodies immunospecific for VPIs, and kits comprising the aforesaid.



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INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 G01N33/68 C07K14/47 A61P9/10 A61P25/28 A61K38/17

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 G01N C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, CHEM ABS Data, MEDLINE, EMBASE, BIOSIS, EMBL, WPI Data, PAJ, INSPEC

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	MATTILA K M ET AL: "Altered blood-brain-barrier function in Alzheimer's disease?" ACTA NEUROLOGICA SCANDINAVICA, vol. 89, no. 3, 1994, pages 192-198, XP001011873 ISSN: 0001-6314	1-5
A	abstract page 193, left-hand column, line 3 -right-hand column, line 3 page 194, right-hand column, paragraph 2 page 195, left-hand column, paragraph 5 -page 196, paragraph 3 --- -/--	6,7

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

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P document published prior to the international filing date but later than the priority date claimed

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X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

8 document member of the same patent family

Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/01106

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 98 27226 A (NOVA MOLECULAR INC) 25 June 1998 (1998-06-25) abstract page 2, line 11 -page 4, line 20 page 8, line 25 -page 9, line 25; example 1 claims 1-8	1-7
A	ARAI HIROYUKI ET AL: "No increase in cerebrospinal fluid tau protein levels in patients with vascular dementia." NEUROSCIENCE LETTERS, vol. 256, no. 3, 13 November 1998 (1998-11-13), pages 174-176, XP001011876 ISSN: 0304-3940 the whole document	1-7
A	BLENNOW K ET AL: "Cerebrospinal fluid 'neuronal thread protein' comes from serum by passage over the blood-brain barrier." NEURODEGENERATION, vol. 4, no. 2, 1995, pages 187-193, XP001011872 ISSN: 1055-8330 abstract page 188, right-hand column, line 1 - line 8 page 188, right-hand column, paragraphs 4,5 page 189, left-hand column, paragraph 7 -page 191, left-hand column, line 20	1-7
A	WO 95 30433 A (RES DEV FOUNDATION) 16 November 1995 (1995-11-16) abstract page 1 -page 4 claims 5-10	1
A	LEVY, EFRAT ET AL: "Stroke in Icelandic patients with hereditary amyloid angiopathy is relate to a mutation in the cystatin C gene, an inhibitor of cysteine proteases" J. EXP. MED. (1989), 169(5), 1771-8, XP001011800 the whole document	1,6

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01106

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>ABRAHAMSON M ET AL: "MOLECULAR CLONING AND SEQUENCE ANALYSIS OF CDNA CODING FOR THE PRECURSOR OF THE HUMAN CYSTEINE PROTEINASE INHIBITOR CYSTATIN C" FEBS LETTERS, NL, ELSEVIER SCIENCE PUBLISHERS, AMSTERDAM, vol. 216, no. 2, 1 June 1987 (1987-06-01), pages 229-233, XP002038720 ISSN: 0014-5793 abstract page 232, right-hand column, paragraph 2</p>	1,6
X	<p>WATANABE T K ET AL: "CLONING AND CHARACTERIZATION OF TWO NOVEL HUMAN CDNAS (NELL1 AND NELL2) ENCODING PROTEINS WITH SIX EGF-LIKE REPEATS" GENOMICS, ACADEMIC PRESS, SAN DIEGO, US, vol. 38, no. 3, 15 December 1996 (1996-12-15), pages 273-276, XP002064052 ISSN: 0888-7543 abstract -& DATABASE SWISS-PROT 'Online! ID: NEL2_HUMAN AC: Q99435, XP002186525 cited in the application abstract</p>	13-23
X	<p>EP 0 796 913 A (OTSUKA PHARMA CO LTD) 24 September 1997 (1997-09-24) abstract</p>	13-23
X	<p>OYASU MIHO ET AL: "Immunocytochemical localization of a neuron-specific thrombospondin-1-like protein, NELL2: Light and electron microscopic studies in the rat brain." MOLECULAR BRAIN RESEARCH, vol. 76, no. 1, 10 March 2000 (2000-03-10), pages 151-160, XP002949478 ISSN: 0169-328X abstract</p>	13-23
X	<p>KURODA SHUN'ICHI ET AL: "Biochemical characterization and expression analysis of neural thrombospondin-1-like proteins NELL1 and NELL2." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, vol. 265, no. 1, 11 November 1999 (1999-11-11), pages 79-86, XP001051695 ISSN: 0006-291X abstract</p>	13-23

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01106

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	KACZOREK M ET AL: "MOLECULAR CLONING AND SYNTHESIS OF BIOLOGICALLY ACTIVE HUMAN TISSUE INHIBITOR OF METALLOPROTEINASES IN YEAST" BIO-TECHNOLOGY (NEW YORK), vol. 5, no. 6, 1987, pages 595-598, XP001042262 ISSN: 0733-222X the whole document -& DATABASE SWISS-PROT 'Online! ID: TIM1_HUMAN AC: P01033; Q14252, XP002186526 cited in the application abstract	13-23
X	MUN-BRYCE, S. ET AL.: "Matrix Metalloproteinases in Cerebrovascular Disease" JOURNAL OF CEREBRAL BLOOD FLOW AND METABOLISM, vol. 18, 1998, pages 1163-1172, XP001051471 the whole document	8-46, 55-62
X	WANG X ET AL: "SUBTRACTIVE CLONING IDENTIFIES TISSUE INHIBITOR OF MATRIX METALLOPROTEINASE-1 (TIMP-1) INCREASED GENE EXPRESSION FOLLOWING FOCAL STROKE" STROKE, AMERICAN HEART ASSOCIATION, DALLAS TX, US, vol. 29, no. 2, February 1998 (1998-02), pages 516-520, XP001051492 ISSN: 0039-2499 abstract	8-46
X	ROMANIC A M ET AL: "MATRIX METALLOPROTEINASE EXPRESSION INCREASES AFTER CEREBRAL FOCAL ISCHEMIA IN RATS INHIBITION OF MATRIX METALLOPROTEINASE-9 REDUCES INFARCT SIZE" STROKE, AMERICAN HEART ASSOCIATION, DALLAS TX, US, vol. 29, no. 5, 1998, pages 1020-1030, XP001051490 ISSN: 0039-2499 abstract	8-46

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 01/01106

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>REID ROBERT A ET AL: "Identification and characterization of the human cell adhesion molecule contactin." MOLECULAR BRAIN RESEARCH, vol. 21, no. 1-2, 1994, pages 1-8, XP001052602 ISSN: 0169-328X abstract -& DATABASE SWISS-PROT 'Online! ID: CONT_HUMAN AC: Q12860; Q12861; Q14030, XP002186527 cited in the application abstract</p>	13-23
X	<p>SAKURAI T ET AL: "INDUCTION OF NEURITE OUTGROWTH THROUGH CONTACTIN AND NR-CAM BY EXTRACELLULAR REGIONS OF GLIAL RECEPTOR TYROSINE PHOSPHATASE BETA" THE JOURNAL OF CELL BIOLOGY, ROCKEFELLER UNIVERSITY PRESS, US, vol. 136, no. 4, 24 February 1997 (1997-02-24), pages 907-918, XP001051425 ISSN: 0021-9525 abstract</p>	13-23
X	<p>CHO HIROYUKI ET AL: "Biphasic changes in F3/contactin expression in the gerbil hippocampus after transient ischemia." EXPERIMENTAL BRAIN RESEARCH, vol. 122, no. 2, 1998, pages 227-234, XP001024392 ISSN: 0014-4819 abstract</p>	8-46
X	<p>WO 95 35373 A (JOLLA CANCER RES FOUND) 28 December 1995 (1995-12-28) abstract</p>	13-23
X	<p>WO 96 37776 A (SUGEN INC) 28 November 1996 (1996-11-28) abstract; claims 1-16</p>	13-23
P, X	<p>WO 00 70099 A (MITOKOR ;BECKER K DAVID (US); DAVIS ROBERT E (US); HWANG JUNG JOO) 23 November 2000 (2000-11-23) abstract</p>	8-46
	<p>---</p> <p>-/--</p>	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 01/01106

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>LITTLE S P ET AL: "ZYME, A NOVEL AND POTENTIALLY AMYLOIDGENIC ENZYME CDNA ISOLATED FROM ALZHEIMER'S DISEASE BRAIN" JOURNAL OF BIOLOGICAL CHEMISTRY, AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, BALTIMORE, MD, US, vol. 272, no. 40, 1997, pages 25135-25142, XP002926885 ISSN: 0021-9258 abstract -& DATABASE SWISS-PROT 'Online! ID: KLK6_HUMAN AC: Q92876, XP002186528 cited in the application abstract</p>	8-46
X	<p>YAMASHIRO K ET AL: "Molecular cloning of a novel trypsin-like serine protease (neurosin) preferentially expressed in brain" BIOCHIMICA ET BIOPHYSICA ACTA. GENE STRUCTURE AND EXPRESSION, ELSEVIER, AMSTERDAM, NL, XP002075096 ISSN: 0167-4781 abstract</p>	13-23
X	<p>YOUSEF G M ET AL: "MOLECULAR CHARACTERIZATION OF ZYME/PROTEASE M/NEUROSIN (PRSS9), A HORMONALLY REGULATED KALLIKREIN-LIKE SERINE PROTEASE" GENOMICS, ACADEMIC PRESS, SAN DIEGO, US, vol. 62, no. 2, 1999, pages 251-259, XP001051426 ISSN: 0888-7543 abstract</p>	13-23
X	<p>GOHLKE ULRICH ET AL: "The C-terminal (haemopexin-like) domain structure of human gelatinase A (MMP2): Structural implications for its function." FEBS LETTERS, vol. 378, no. 2, 1996, pages 126-130, XP002057541 ISSN: 0014-5793 the whole document -& DATABASE SWISS-PROT 'Online! ID: MM02_HUMAN AC: P08253, XP002186529 cited in the application abstract</p>	13-23

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 01/01106

C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	YAMADA T ET AL: "Selective localization of gelatinase A, an enzyme degrading beta-amyloid protein, in white matter microglia and in Schwann cells." ACTA NEUROPATHOLOGICA, vol. 89, no. 3, 1995, pages 199-203, XP001052600 ISSN: 0001-6322 the whole document	8-46
X	WO 95 02045 A (DOCHERTY ANDREW JAMES PENROSE ; CRABBE THOMAS (GB); BAKER TERENCE S) 19 January 1995 (1995-01-19) abstract	13-23
E	WO 01 26671 A (SMITHKLINE BEECHAM PLC ; SMITHKLINE BEECHAM CORP (US)) 19 April 2001 (2001-04-19) abstract	8-46

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 01/01106

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☒ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
All claims relating to (VF-4) VPI-2, VPI-29, VPI-15, VPI-21, VPI-273 and VPI-154
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.1

Although claims 24, 25, or 26 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: Invention 1: Claims 1-7 (partially)

Diagnosis of vascular dementia using VF-4 as marker.

2. Claims: Inventions 2-712: Claims 1-46 (all partially)

Diagnosis or treatment of vascular dementia using one of VF-5 to VF-372 or one of VPI-2 to VPI-273 as marker/target.

3. Claims: Invention 713: 47-54 (fully)

Method of screening for agents effective for the treatment of vascular dementia involving IGF-II

4. Claims: Invention 714: Claims 55-62 (fully)

Method of screening for agents effective for the treatment of vascular dementia involving TIMP-1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 01/01106

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9827226	A	25-06-1998	US	6022683 A	08-02-2000
			AU	5571798 A	15-07-1998
			AU	5675798 A	15-07-1998
			EP	0948647 A1	13-10-1999
			EP	0946753 A2	06-10-1999
			WO	9827226 A2	25-06-1998
			WO	9827227 A2	25-06-1998
WO 9530433	A	16-11-1995	US	5677277 A	14-10-1997
			AU	693207 B2	25-06-1998
			AU	2584995 A	29-11-1995
			CA	2190027 A1	16-11-1995
			EP	0752881 A1	15-01-1997
			IL	113347 A	30-11-1999
			JP	10500293 T	13-01-1998
			NZ	287205 A	29-07-1999
			TW	414800 B	11-12-2000
			WO	9530433 A1	16-11-1995
			ZA	9503488 A	04-11-1996
EP 0796913	A	24-09-1997	JP	9308492 A	02-12-1997
			CA	2200371 A1	19-09-1997
			EP	0796913 A2	24-09-1997
			US	6005088 A	21-12-1999
			US	6166190 A	26-12-2000
			US	5831058 A	03-11-1998
WO 9535373	A	28-12-1995	AU	2824195 A	15-01-1996
			WO	9535373 A2	28-12-1995
WO 9637776	A	28-11-1996	US	5766922 A	16-06-1998
			AU	5927096 A	11-12-1996
			WO	9637776 A1	28-11-1996
WO 0070099	A	23-11-2000	AU	5150300 A	05-12-2000
			WO	0070099 A2	23-11-2000
WO 9502045	A	19-01-1995	AU	7128494 A	06-02-1995
			WO	9502045 A2	19-01-1995
WO 0126671	A	19-04-2001	WO	0126671 A1	19-04-2001

